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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,971	04/27/2005	Andrew J Caton	WST108AUSA	4656

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HOWSON AND HOWSON
SUITE 210
501 OFFICE CENTER DRIVE
FT WASHINGTON, PA 19034

EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,971	CATON, ANDREW J	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-6,8-12,14,15,17,20 and 46-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-6,8-12,14,15,17,20 and 46-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response to the restriction requirement received on 8/2/07 has been entered. Claims 1, 7, 13, 16, 18-19, and 21-45 have been canceled, and new claims 46-55 have been added. Claims 2-6, 8-12, 14-15, 17, 20, and 46-55 are currently pending in the instant application. Application election of the subject matter of Group II is acknowledged. Since applicant did not indicate that the election was made with traverse or provide any arguments traversing the grounds for restriction, the election is considered to have been made without traverse. It is further noted that applicant has amended claims 2-6, 8-12, and 14-15 to correspond to the subject matter of Group II. Thus, claims 2-6, 8-12, 14-15, 17, 20, and 46-55 are drawn to the elected subject matter and are currently under examination. An action on the merits follows.

Priority

Applicant's preliminary amendment filed on 4/27/05 added a benefit of priority paragraph to page 1 of the specification. Benefit of priority to International application PCT/US03/031519, filed 10/27/03, and further to US provisional application 60/422,389, filed 10/30/02, is acknowledged. The effective filing date for this application is 10/30/02.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 8/28/06 is in compliance with the provisions of 37 CFR 1.97 and 1.98. Accordingly, the information disclosure statement has been considered by the examiner and an initialed and signed copy of the 1449 is attached to this action.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2-6, 8-12, 14-15, 17, 20, and 46-55 are rejected under 35 U.S.C. 102(b) as being anticipated by Jordan et al. (April, 2001) Nature Immunology, Vol. 2(4), 301-306. Please note that while the instant inventor, Andrew Caton, is one of the authors of Jordan et al., this reference was published more than 1 year before the effective filing date for this application and therefore cannot be overcome by a declaration under 37 CFR 1.131 or 132.

Jordan et al. teaches the double transgenic mice TS1XHACII and TS1(SW)XHACII, produced by breeding first and second single transgenic mice, where the first and second mice are either TS1 and HACII or TS1(SW) and HACII respectively (Jordan et al., pages 304-305 and Figure 4). The TS1 mouse comprises a transgene for the MHC class II restricted TCR TS1 which has high affinity for the HA S1 peptide and low affinity for the HA S1 peptide analog S1(SW) which differs from the S1 peptide by two amino acid substitutions (Jordan et al., page 304). Note

that the S1 peptide has the sequence identified in SEQ ID NO:1 and the S1(SW) peptide has the sequence identified in SEQ ID NO:2 (Jordan et al., see page 306 for the sequences of the S1 and S1(SW) peptides). The TS1(SW) mouse comprises a transgene for the MHC class II restricted TCR TS1 which has high affinity for the HA S1(SW) peptide and low affinity for the HA S1 peptide (Jordan et al., page 304-305). The HACII mouse contains a transgene encoding PR8 HA under control of the MHC class II Eα promoter, expresses high amounts of HA on class II positive cells, and further present the S1 peptide for TCR binding (Jordan et al., pages 305-306). The resulting double transgenic TS1XHACII and TS1(SW)XHACII mice are identical in structure to those claimed in the instant application and disclosed in the working examples of the instant specification.

While Jordan et al. provides some analysis of the features of the TS1XHACII and TS1(SW)XHACII mice, Jordan et al. does not report on whether these mice exhibit any autoimmune phenotype, including inflammatory arthritis characterized by inflamed joints with bone resorption, mononuclear cell infiltrates and pannus formation, or the penetrance of the inflammatory arthritis. However, as the double transgenic mice taught by Jordan et al. are identical in structure to the claimed invention, the claimed property wherein the mammal develops symptoms, such as inflamed joints with bone resorption, mononuclear cell infiltrates and pannus formation associated with inflammatory arthritis is considered inherent. "When the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or *In re Best*, 195 USPQ 430, 433 (CCPA 1997). The applicant is further reminded that there is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention.

Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003). Therefore, by teaching double transgenic mice with the identical structure to those claimed, Jordan et al. anticipates the instant invention as claimed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-6, 8-12, 14-15, 17, 20, and 46-55 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for TS1 X HACII double transgenic mice on a BALB/C background which exhibit high penetrance of spontaneous inflammatory arthritis and TS1(SW) X HACII double transgenic mice on a BALB/C background which exhibit low penetrance of spontaneous inflammatory arthritis, does not reasonably provide enablement for any non-human mammal model of any autoimmune disease where the non-human mammal is transgenic for any combination of an MHC class II restricted TCR and a selected peptide that binds to said TCR and which is selectively expressed by MHC class II positive APCs, wherein the mammal develops the phenotypic symptoms of an autoimmune disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims read broadly on transgenic non-human mammals which express an MHC class II-restricted TCR and which selectively express a selected peptide on MHC class II positive APCs and which develop an autoimmune disorder. It is noted that non-human mammals include

horses, dogs, cats, zebras, rodents, and even platypuses. The specification broadly discloses a number of autoimmune disorders including Crohn's disease, multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosis, inflammatory bowel disease, nephritis, autoimmune thyroiditis, reactive arthritis, ankylosing spondylitis, scleroderma, polymyositis, dermatomyositis, psoriasis, Wegener's granulomatosis, ulcerative colitis, Sjogren's syndrome, sarcoidosis, and insulin dependent diabetes mellitus (IDDM). The specification also discloses several MHC class II TCR including the mouse TCR TS1 and TS1(SW) which bind to the HA determinant S1, a mouse TCR specific for cytochrome C, a mouse TCR specific for hemoglobin, and a mouse TCR specific for Hen egg lysosyme. However, aside from these general disclosures, the specification is largely drawn to the development and characterization of transgenic mice whose genome comprises a TS1 or TS1(SW) TCR transgene and an HA transgene operably linked to either a constitutive promoter or a tissue specific MHC class II Eα promoter produced by mating single transgenic TS1 or TS1(SW) mice with HA104 (constitutive promoter) or HACII (Eα promoter) single transgenic mice. The working examples provide a detailed analysis of these mice and disclose that TS1 X HACII mice exhibit "high penetrance" of spontaneously arising autoimmune symptoms resembling rheumatoid arthritis including inflamed joints with bone resorption, mononuclear cell infiltrates and pannus formation associated with inflammatory arthritis, and TS1 (SW) X HACII mice exhibit “low penetrance” of the same symptoms. In contrast, the TS1 X HA104 mice which systemically express HA, while exhibiting some evidence of autoimmunity in the form of the presence of autoreactive CD4+ T cells and some non-specific inflammation, did not exhibit the same collection of symptoms associated with

inflammatory arthritis as the double transgenic mice with selective HA expression in MHC class II positive APCs.

The specification fails to provide an enabling disclosure for double transgenic non-human mammals which exhibit high or low penetrance of any autoimmune disorder other than the aforementioned TS1XHACII or TS1(SW)XHACII double transgenic mice. As noted above, the specification briefly notes the existence of several MHC class II restricted TCR which have been cloned from mouse T cells and which have been introduced into transgenic mice, including a mouse TCR specific for cytochrome C, a mouse TCR specific for hemoglobin, and a mouse TCR specific for Hen egg lysosyme, citing various prior art references not of record. However, the specification is silent as to the possible phenotype of any double transgenic mice made by mating these single transgenic mice with transgenic mice expressing any natural, recombinant, or synthetic determinant which binds to the transgenic TCR in MHC class II positive APCs. The specification suggests that such double transgenic mice will exhibit some symptoms of an autoimmune disease, but fails to provide any particular guidance as to what the nature of those symptoms might be for any combination of TCR and peptide other than the TS1 or TS1(SW) TCR and the HA S1 peptide. In particular, it is noted that cytochrome C and hemoglobin are naturally expressed self-antigens already present in the single transgenic mice. The prior art does not report that such mice expressing TCR specific for cytochrome C or hemoglobin exhibit any symptoms of autoimmune disease. Further, while the prior art does teach the production of various MHC class II restricted HEL-TCR X HEL mice, the prior art shows that although autoreactive anti-HEL CD4+ T cells are present in these mice, the ability of these cells to induce symptoms associated with autoimmune disease is limited. For example, Akkaraju et al. teaches

the production of 5 different double transgenic HEL-TCR/HEL mice in which mice transgenic for an MHC class II restricted TCR specific for HEL are mated to transgenic mice expressing HEL either systemically or ubiquitously, or under control of a thyroid or pancreatic specific promoter. While some infiltration of the thyroid or pancreas is observed in the organ specific HEL expressing mice, the inflammation does not result in any cell death or the development of thyroiditis or diabetes in these mice (Akkaraju et al. (1997) Immunity, Vol. 7, 255-271). Akkaraju et al. further teaches that the fate, i.e. clonal deletion versus tolerance, and the responsiveness of autoreactive CD4+ T cells that escape clonal deletion in the double transgenic mice is dependent on many factors including the level of "self-antigen" expression, the sites of antigen expression, and even the genetic background of the mice (Akkaraju et al., pages 255, 263-264 and 267, Figure 9). In particular, regarding genetic background, Akkaraju et al. teaches that while BALB/C double transgenic HA-TCRX HA mice which express HA in the pancreas did not exhibit insulinitis, expression of the same TCR and HA transgenes in the B10 background resulted in mice which exhibited both insulinitis and diabetes. Figure 9 on page 267 of Akkaraju et al. is particularly interesting as it compares the level of CD4+ tolerance observed by Akkaraju et al. and other published studies to different neo-self and recombinant self-antigens. This figure clearly shows the complexity of CD4+ T cell tolerance induction in double transgenic mice. From the teachings of Akkaraju et al., it can be seen that the phenotype of any double transgenic TCR/ antigen mouse on any genetic background is affected by many factors and cannot be predicted *a priori*. The teaching of Akkaraju et al. further demonstrate that the existence of autoreactive CD4+ T cells in the periphery does not predictably result in spontaneous autoimmunity. Thus, based on the state of the art of spontaneous autoimmunity in

double transgenic MHC class II restricted TCR/antigen mice, the unpredictability of determining *a priori* whether the expression of any combination of MHC class II restricted TCR and antigen in any genetic mouse background will result in spontaneous development of any autoimmune disorder or disease, the breadth of the claims, and the limitation of the working examples to TS1 X HACII double transgenic mice on a BALB/C background which exhibit high penetrance of spontaneous inflammatory arthritis and TS1(SW) X HACII double transgenic mice on a BALB/C background which exhibit low penetrance of spontaneous inflammatory arthritis, it would have required undue experimentation for the skilled artisan to make and use the full scope of the claimed transgenic non-human mammalian models of autoimmune disease.

The specification further fails to provide an enabling disclosure for making any non-human double transgenic MHC class II restricted TCR X antigen mammal which spontaneously exhibits an autoimmune disease other than a transgenic mouse comprising the TS1 or TS1(SW) TCR transgene and the HA transgene operatively linked to the Eα promoter on a BALB/C background. As discussed above, the specification's disclosure, while providing several generic paragraphs which broadly disclose the generation of non-human transgenic mammals, is largely drawn to the generation of transgenic mice. Further, as also noted above, the specification's disclosure of TCR molecules for use in the instant mammals is limited to mouse TCRs. The specification provides no description or guidance for MHC class II restricted TCR alpha and beta sequences with specificity for any self-antigen or neo-self antigen from any non-mouse species, such as horse, camel, elephant, or lion. The specification also fails to provide any particular description of the sequences of any self-antigen, whether natural or synthetic, from any non-mouse mammal. In addition, the state of the art at the time of filing, as discussed in detail above,

teaches the generation of transgenic mice for studies of CD4+ T cell tolerance and autoimmunity, and does not teach or suggest methods for producing double transgenic dogs, sheep, foxes, or giraffes. Further, as the prior art of record as evidenced by Akkaraju et al. demonstrates the unpredictability in mice of predicting the phenotype resulting from expression of a "self antigen" and an MHC class II restricted TCR specific for that self antigen, the skilled artisan would not have been able to predict without undue experimentation whether the expression of any particular combination of MHC class II restricted TCR and self antigen in any non-human mammal would result in any symptoms of any autoimmune disease.

In addition, it is noted that claims 4-5, 8-10, 50 and 52, while broadly reciting the genus of non-human mammals, contain the limitation where the TCR is the TS1 or TS1(SW) TCR. Both the TS1 and TS1(SW) TCR are TCR derived from mouse T cells which developed in mice and are restricted to mouse MHC class II. The specification does not report that these TCR are capable of binding any species of MHC class II molecules other than mouse. Further, based on the process of T cell development, these TCR molecules were specifically selected for affinity to a specific mouse MHC class II molecule. It would be highly unlikely that such TCR molecules would recognize and bind with sufficient affinity and avidity any MHC class II molecule from any other mammalian species. As such, the skilled artisan at the time of filing would not have predicted that the expression of TS1 or TS1(SW) in any non-mouse species would generate any CD4+ T cells expressing TS1 or TS1(SW) since positive selection requires substantive binding of the mouse TCR with the endogenous non-mouse MHC class II molecules.

Therefore for the reasons set forth above, it would have required undue experimentation at the time of filing to make and use the full scope of the non-human transgenic mammals as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 50 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 50 depends on claim 20 and recites "said determinant"; however, there is no antecedent basis for "said determinant" in either claim 50 or 20.

No claims are allowed.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for

electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633